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New Stent Technologies

Yukio Ozaki, Andonis G. Violaris, and Patrick W. Serruys

Coronary stents were developed to overcome the two main limitations of balloon angioplasty, acute occlusion and long-term restenosis. Coronary stents can tack back intimal flaps and seal the dissected vessel wall, thereby treating acute or threatened vessel closure after unsuccessful balloon angioplasty. After successful balloon angioplasty, stents can prevent late vessel remodeling (chronic vessel recoil) by mechanically enforcing the vessel wall and resetting the vessel size, resulting in a low incidence of restenosis. All currently available stents are composed of metal, and the long-term effects of their implantation in the coronary arteries are still not clear. Because of the metallic surface, they are also thrombogenic; therefore, rigorous antiplatelet or anticoagulant therapy is theoretically required. Furthermore, they have an imperfect compromise between scaffolding properties and flexibility, resulting in an unfavorable interaction between stents and unstable or thrombus-laden plaque. Finally, they still induce substantial intimal hyperplasia that may result in restenosis. Future stents can be made less thrombogenic by modifying the metallic surface or coating it with an antithrombotic agent or a membrane eluting an antithrombotic drug. The unfavorable interaction with the unstable plaque and the thrombus burden can be overcome by covering the stent with a biological conduit, such as a vein, or a biodegradable material that can be endogenous, such as fibrin, or exogenous, such as a polymer. Finally, the problem of persisting induction of intimal hyperplasia may be overcome with the use of either a radioactive stent or a stent eluting an antiproliferative drug.

CORONARY stents were developed to overcome the two main limitations of balloon angioplasty, acute occlusion and long-term restenosis. Coronary stents can tack back intimal flaps and seal the dissected vessel wall, thereby treating acute or threatened vessel closure after unsuccessful balloon angioplasty. After successful balloon angioplasty, stenting can prevent late vessel remodeling (chronic vessel recoil) by mechanically enforcing the vessel wall and resetting the vessel size, resulting in a low incidence of restenosis. These theoretical advantages of coronary stenting have been tested in two major randomized trials.[1,2] Both the Belgium Netherlands Stent Study (Benestent) and Stent Restenosis Study (STRESS) confirmed the theoretical advantages of coronary stenting by showing a reduction in angiographic restenosis and clinical events during follow-up examination.[1,2] This reduction in restenosis was achieved by a greater luminal gain despite the accommodation of a greater absolute loss in lumen diameter in the stent group, suggesting greater neointimal hyperplasia in this group. The reduction in long-term restenosis was counterbalanced by bleeding complications related to the anticoagulant therapy. Therefore, a number of limitations have to be overcome before coronary stenting achieves its full potential.

CURRENTLY AVAILABLE STENTS

The currently available stents, a description of their design, and the year of their clinical introduction are listed in Table 1 and are shown in Fig 1. In the absence of prospective randomized interstent comparative trials, it is difficult to draw conclusions on the relative merits and demerits of each stent design. However, individual experience and registry data from each stent allow preliminary impressions to be made on the advantages and limitations of each stent.

Wallstent

The Wallstent (Schneider, Bulach, Switzerland) was the pioneer of stents[3-5] through which we learned the risk profile and indications for coronary stenting and the necessity and adverse effects of antithrombotic measures. The new less-shortening Wallstent has been developed recently with a change in the braiding angle; and results of the first clinical implantation of this second generation stent in coronary vein grafts have been promising.[6] The unique advantages of the Wallstent include the extensive range of diameters and lengths available, thereby allowing the Wallstent to be used for the management of long spiral dissections[7] and for vessel reconstruction.[8] The sheathed "balloon-

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Table 1. Currently Available Stents Undergoing Clinical Evaluation

Coronary Stent	Design	Deployment	Premounted	Delivery	Diameter (mm)	Length (mm)	First Clinical Implantation
Wallstent	Wire mesh	Self-expanding	Balloon not required	Over-the-wire	3.5-6.0	12-42	1986 1991 (less-shortening)
Palmaz-Schatz	Slotted tube	Balloon-expandable	Premounted and unmounted	Over-the-wire and both	3.0-4.0	8-18	1988 1994 (heparin-coated)
Gianturco-Roubin	Incomplete coil clam-shell loop	Balloon-expandable	Premounted	Over-the-wire	2.5-4.0	20-40	1989 (GR-I) 1995 (GR-II)
Wiktor	Sinusoidal helical coil	Balloon-expandable	Premounted	Over-the-wire or monorail	3.0-4.5	16	1991 1995 (short-wave)
Multi-Link	Multiple rings with multiple links	Balloon-expandable	Premounted	Over-the-wire	3.0-3.5	15	1993
Cordis	Sinusoidal helical coil	Balloon-expandable	Premounted	Over-the-wire	3.0-4.0	15	1994
AVE Micro	Zigzag axial struts	Balloon-expandable	Premounted	Monorail	2.5-4.0	6-36	1994 (Micro-I) 1995 (Micro-II)
NIR	Expandable uniform cellular mesh	Balloon-expandable	Unmounted	Both	2.0-5.0	9-32	1995

less" delivery system in combination with the free, unconnected wire-mesh design, render the Wallstent one of the most trackable, pushable, and flexible stents for negotiating tortuous vessel and passing through proximally deployed stents (Fig 2). Furthermore, recent modification of the delivery system allows recapture of the stent before final deployment and also allows

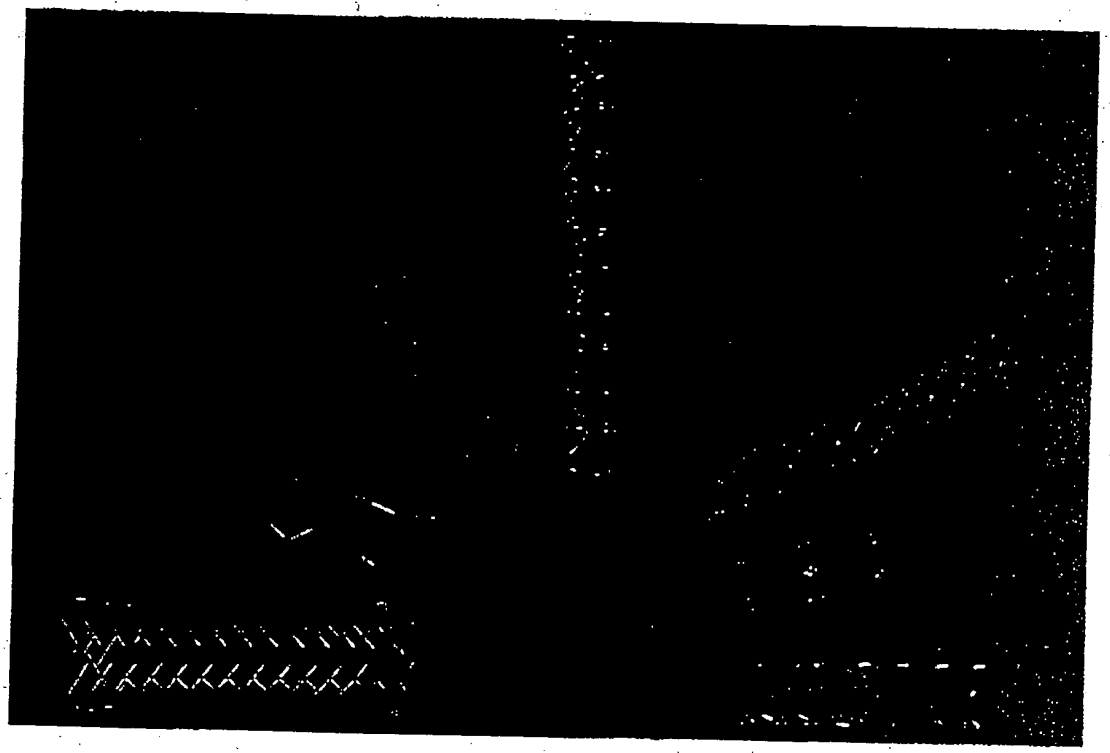

Fig 1. Coronary stents that have undergone clinical evaluation are shown clockwise from the left: Wallstent, Palmaz-Schatz, Wiktor, Gianturco-Roubin, Cordis, AVE Micro, and ACS Multi-Link. (Reprinted with permission.[2])

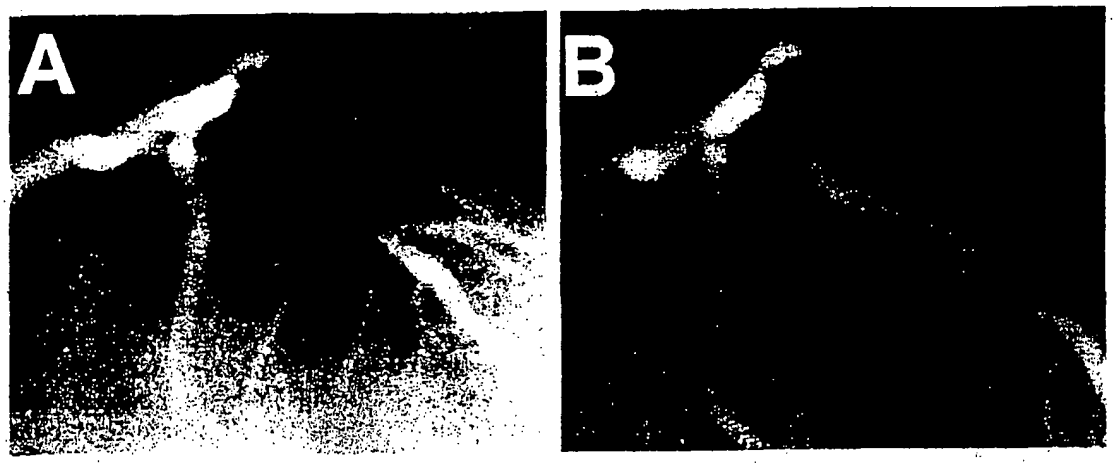

Fig 2. (A) Long complex stenosis in left anterior descending artery before intervention. (B) Final angiographic outcome after the deployment of the new less-shortening Wallstent. Note the smooth contour stented segment with no loss of side branches and the absence of vessel sprinting that may be obseved after the deployment of a more rigid stent.

improved positioning, raising the possibility for the use of shorter Wallstents in clinical practice. Its fine cross-hatched mesh design provides excellent scaffolding properties particularly well-suited to entrap friable material in diffusely diseased vein grafts. Additionally, enforced mechanical remodeling produced by oversizing Wallstent implantation conveys a favorable 6-month clinical and angiographic outcome in both stenosis and total occlusions in native coronary arteries.[7,8] Its primary limitations are the longitudinal shortening of the stent on radial expansion and motion of the stent during retraction of the rolling membrane, thus rendering the stent less suitable for ostial lesions.

Palmaz-Schatz Stent

The Palmaz-Schatz stent (Johnson & Johnson Interventional Systems, Warren, NJ) has been extensively investigated in a broad range of coronary lesions.[9-18] It is the only stent to date to have completed prospective randomized trials comparing the clinical and angiographic outcome with that of balloon angioplasty.[1,2] The angiographic results after Palmaz-Schatz stent implantation are predictable, and the slotted-tube design allows the performance of high-pressure intrastent balloon inflations without risk of structural deformation. However, the low radiopacity of the Palmaz-Schatz stent can render the positioning of a noncompliant balloon for postdeployment, high-pressure, intrastent inflations difficult. Additionally, a higher incidence of restenosis has been reported at the site of the central articulation.[19] To overcome this limitation, a recent model has been developed without the central articulation (spiral articulation design). This model has a higher radiopacity compared with that of the standard single articulation design. The availability of a free, unmounted Palmaz-Schatz stent that can be crimped by the operator on any balloon provides more procedural versatility and results in a lower profile during stent delivery. However, it does increase the risk of losing the stent during deployment.

Gianturco-Roubin Stent

Before obtaining Food and Drug Administration (FDA) approval for noninvestigational clinical use, most of the clinical data on the Gianturco-Roubin stent (Cook, Inc, Bloomington, IN) was gathered in single and multicenter registries in the United States.[20-25] The indication for the Gianturco-Roubin stent for which most data have been gathered is for the bailout of subocclusive and occlusive dissections after balloon angioplasty in native coronary arteries. The data gathered compare well with the data from historical controls treated by repeated and prolonged balloon angioplasty alone. The results of the first randomized trial of the Gianturco-Roubin stent in bailout therapy (Gianturco-Roubin stent in Acute Closure Evaluation [GRACE]) are awaited with interest.[26] The principle advantages of the Gianturco-Roubin

stent include its range of lengths and longitudinal flexibility. Although the relatively large interstrut intervals of 1 mm raise questions over the suitability of this stent for the management of friable vein graft lesions, the advantages of the Gianturco-Roubin stent design include minimal risk of "jailing" side branches and the potential to perform coronary interventional procedures in side branches through the interstrut spaces. Whereas this stent excels in long dissections in curved coronary segments (Fig 3), its more generalized use was hindered by the high profile of the first generation. The new generation flex-II stent overcomes these problems with a lower profile and a higher visibility.

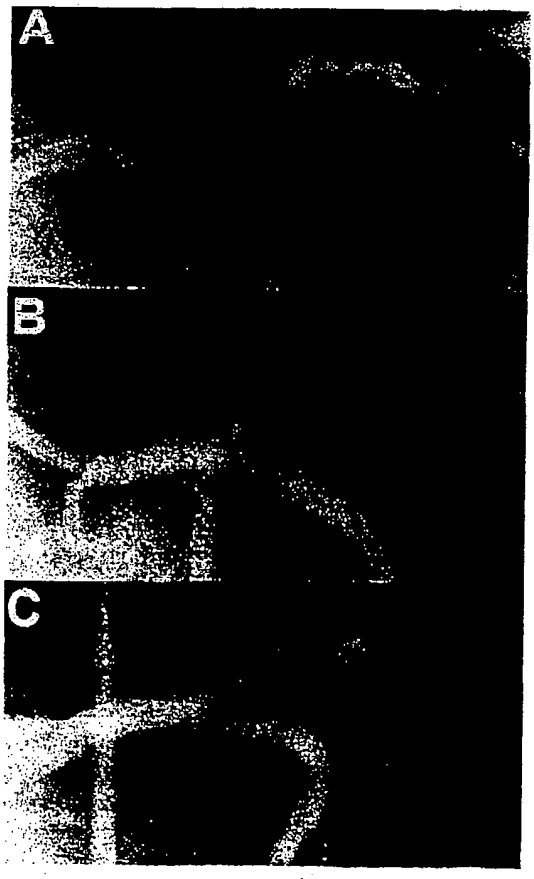

Fig 3. (A) Dissection after balloon angioplasty in the proximal left anterior descending artery is shown. (B) After delivery of a Gianturco-Roubin Flexstent through a Superflow 8-French Judkins guiding catheter (Cordis) to the target vessel, the radiopaque markers (located 1 mm proximal and distal to the stent extremities) facilitate the final positioning of the stent before inflation of the delivery balloon. (C) Contrast angiography poststent deployment shows preservation of the vessel curvature in the stented segment. (Reprinted with permission.[7])

Wiktor Stent

The available clinical data on the Wiktor stent (Medtronic, Minneapolis, MN) arises from observational studies and registry data,[27-30] the principle registry of which has been in the management of restenotic lesions. Similar to the Gianturco-Roubin stent, the Wiktor stent is a coil stent that offers marked flexibility and, thus, conformability with the vessel curvature. However, also similar to the Gianturco-Roubin stent, the Wiktor stent is unlikely to excel in the treatment of friable vein grafts because of the large interstrut interval and the subsequently reduced scaffolding properties. The radiopacity of the Wiktor stent allows exquisite positioning of the stent in ostial and focal lesions, and the flexibility of the stent makes it suitable for short dissections on curved coronary segments. The recent introduction of the option of a monorail delivery system improves the user-friendliness of the device. The limitations of the initial prototype of the Wiktor stent included the availability of only one length and the limited scaffolding properties with the potential for the protrusion of intimal flaps through the interstrut intervals. These limitations have been overcome by the new generation, short-waveform Wiktor stent, although the radiopacity of this tantalum stent can still interfere with online quantitative angiographic analysis of the stented segment.[31]

Multi-Link Stent

At present, the ACS Multi-Link stent (Advanced Cardiovascular Systems, London, UK) has the least clinical experience of the currently available stents, having just completed its first 100-patient registry conducted at five European centers.[32] The advantages of this new stent include the flexibility and low profile of the sheathed stent and delivery system. Although the Multi-Link stent design manages to provide remarkable scaffolding properties, the metallic burden to the stented vessel remains very low by virtue of the small diameter of the corrugated struts. The limitations of the stent include its radiolucency, which renders the positioning of noncompliant balloons for postdelivery, high-

pressure intrastent inflations very difficult. The current availability of only one length of 15 mm means that the first prototype can only be used for very focal lesions. After some minor modifications, this stent may offer some significant advantages over the earlier generation of stent designs. The attachment of radiopaque tips on the stent would present a significant enhancement.

AVE Micro Stent

The AVE Micro stent (Applied Vascular Engineering, Santa Rosa, CA) is now undergoing clinical evaluation in a large number of countries.[33] The high degree of radiopacity and balloon-expandable deployment should render this stent ideal for exquisite positioning in highly focal and ostial lesions (Fig 4). However, by virtue of the longitudinal (axial) orientation of its eight struts, the 4-mm AVE Micro stent units may be prone to proximal migration and protrusion; therefore, preferably longer, welded AVE Micro stents should be deployed in ostial locations. The customized range of short lengths make the AVE Micro stent ideal as an adjunctive complementary device for multiple stenting, filling in the gaps between longer stents, and improving the inflow or outflow of longer stents. Additionally, the high flexibility and low thrombogenecity of the AVE micro stent make it an ideal stent for bailout management after failed balloon angioplasty.[33] Despite the absence of a protective sheath, the low profile and longitudinal strut orientation make the AVE micro stent one of the easiest stents to pass through other proximally deployed stents. The monorail delivery system increases the user-friendliness of the device, which has a short learning curve. The strong radial support proffered by the thick struts should make the stent suitable for the prevention of recoil and restenosis. However, care should be taken to avoid the positioning of junctions between the unconnected 4-mm units at the site of the minimal lumen diameter of lesions to prevent intimal protrusion. Recent developments include the helicoildal welding of multiple 3-mm-length units (Micro stent-II) to provide multiple lengths of up to 36 mm.

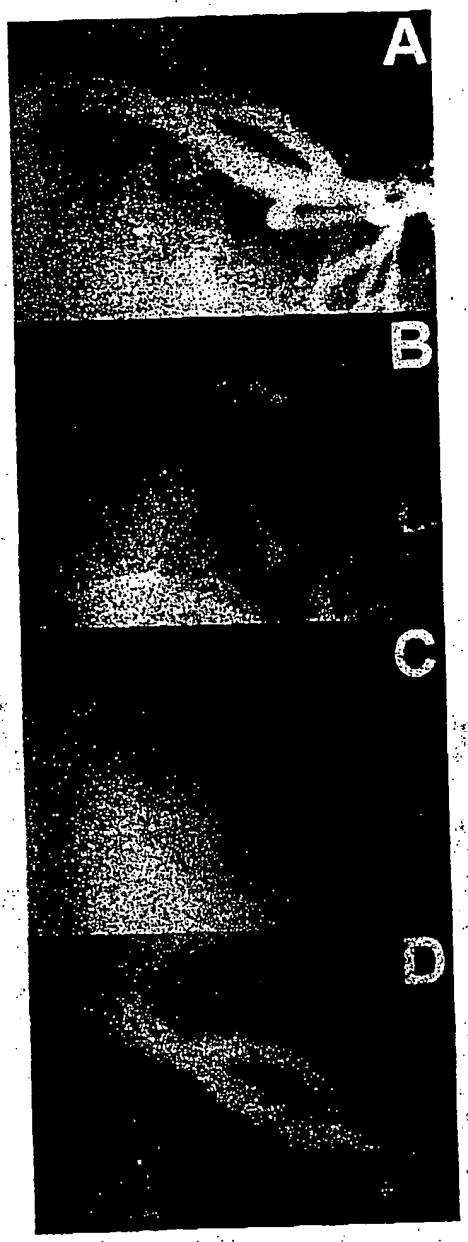

Fig 4. (A) Short dissection in the origin of the left circumflex coronary artery after balloon angioplasty is shown. (B) An AVE Micro stent is delivered to the target vessel through an 8-French Amplatz guiding catheter (Schneider Scientific, Watertown, MA). The two radiopaque markers at the extremities of the stent are clearly seen. (C) After delivery of the stent, the thick radiopaque stainless-steel struts facilitate the precise positioning of a short noncompliant balloon (single marker) within the stent for subsequent high-pressure inflations and optimization of stent deployment. (Reprinted with permission.[3])

Cordis Stent

The Cordis stent (Cordis, Miami, FL) continues to undergo early evaluation in the clinical arena.[31] Similar to the ACS stent, the Cordis stent offers some advantages over the first generation stents by virtue of its low profile, flexibility, and comprehensive scaffolding properties. However, the absence of a protective sheath on the delivery system increases the possibility of stent dislodgement or disruption during delivery. The operator should be aware of the protrusion of the delivery balloon beyond the limits of the Cordis stent if inflations of higher pressure are considered. Although the strongly radiopaque tantalum struts allow exquisite positioning (Fig 5) of the stent in short dissections in curved coronary segments, the radiopacity may pose problems for on-line quantitative angiographic assessment, particularly during assessment of luminal renarrowing at 6-month angiographic follow-up examination.[31] The relative merits of this stent are currently being evaluated in a European multicenter registry and by Hamasaki et al in Japan.[34]

NIR Stent

The NIR stent (Medinol, Tel Aviv, Israel) is a recently developed balloon-expandable stent currently undergoing clinical evaluation in some centers in Israel and Europe. Although this stent has a low radiopacity, the stent has a high flexibility and comes in a wide range of customized sizes (diameter, 2 to 5 mm) and lengths (9 to 32 mm). Balloon-unmounted models allow for the choice of various types of balloon for stent delivery and may spare the usage of an

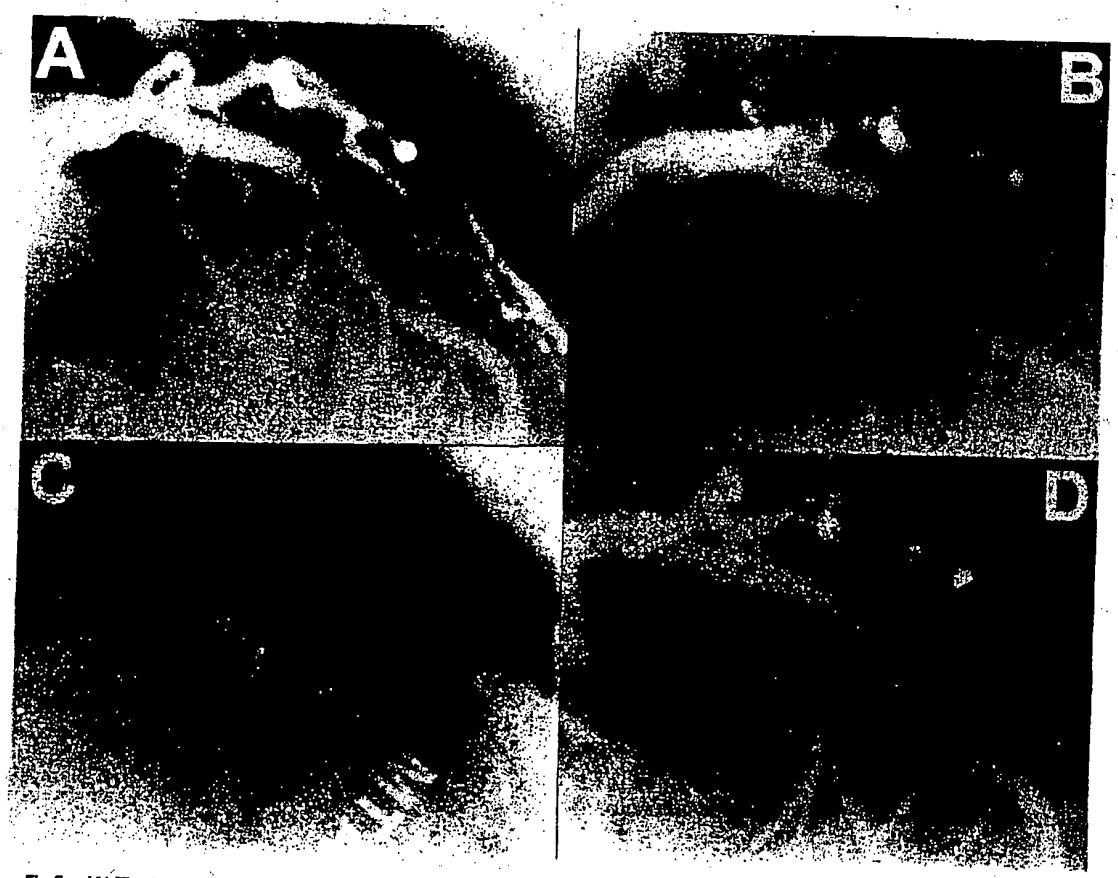

Fig 5. (A) The left coronary artery lesion located at the bifurcation is shown. (B) Postballoon angioplasty dissection type C was clearly seen. (C) Positioning of the Cordis stent was facilitated by the radiopacity of the tantalum struts, which are clearly seen during inflation of the contrast-filled intrastent balloon to 10 atm. (D) Angiography after stent deployment shows the stent struts to be embedded in the vessel wall external to the contour of the contrast-filled lumen.

additional balloon catheter only for stent delivery. A preliminary report indicates a high deployment success rate despite the fact that most of the lesions were difficult to treat because of vessel tortuosity, distal location, and long lesion length.[35] The restenosis rate has not yet been determined.

FUTURE STENTS

All currently available stents are composed of metal, and the long-term effects of their implantation in the coronary arteries are still not clear. Because of the metallic surface, they are thrombogenic; therefore, rigorous antiplatelet or anticoagulant therapy is theoretically required. Furthermore, they represent an imperfect compromise between scaffolding properties and flexibility, resulting in an unfavorable interaction between stent and unstable plaque or thrombus burden. Finally, they still induce substantial intimal hyperplasia that may result in restenosis. Future stents can be made less thrombogenic by modifying the metallic surface or coating it with an antithrombotic agent or a membrane eluting an antithrombotic drug. The unfavorable interaction with the unstable plaque and the thrombus burden can be overcome by covering the stent with a biological conduit, such as a vein, or a biodegradable material that can be endogenous, such as fibrin, or exogenous, such as a polymer. Finally, the problem of persisting induction of intimal hyperplasia may be overcome with the use of either a radioactive stent or a stent eluting an antiproliferative drug.

Coated Stents

Metal coated. In vitro work suggests that surface potential may exert a substantial effect on both the thrombogenicity and antiproliferative effect of metals. High surface potential is associated with pronounced attraction of negatively changed particles such as platelets and plasma proteins, thus resulting in high thrombogenicity. Conversely, however, metals with high surface potential have a substantial antiproliferative effect on fibroblasts, suggesting that, by varying surface charge, we may be able to influence the thrombogenicity and neointimal hyperplasia after stent implantation. One way of accomplishing this would be by modifying the base metal.[36]

Metals can be modified either by galvanization or by ion bombardment. Galvanization involves the electrochemical deposition of metal 3.3 μm in thickness on the stent and results in 100% of the stent surface being covered before stent expansion. Ion bombardment consists of spluttering a thin metal film onto the stent followed by a bombardment with argon ions. The resulting implantation of metal onto the stent surface increases the thickness by 20 nm, and 75% stent surface coverage is required before expansion.

Preliminary experience suggests that coating steel stents with platinum, gold, or copper results in higher in vitro surface potentials but that the incidence of thrombosis in vivo is increased, particularly in stents coated using galvanization.[36] Thus, in contrast to the in vitro suggestion, metal charge does not seem to play a major role in stent thrombogenicity in vivo. Furthermore, a low stent charge appeared to correlate with increased neointimal formation. Therefore, modifying stainless steel stents by covering them with gold, platinum, or copper is unlikely to be the solution to increased thrombogenicity or neointimal hyperplasia.

Cell seeding of stents. Coating of metallic stents with endothelial cells, particularly genetically engineered cells with increased cell surface fibrinolytic activity, may improve their thrombogenic nature. Preliminary work has shown the feasibility of this approach.[37,38] More recently, in vitro work suggests that genetically engineered endothelial cells would allow increased fibrinolysis to be promoted by the surface localization of urokinase.[39] However, questions remain concerning the number of cells that will remain attached under flow conditions and the legal responsibility in case of failure of endothelial cell function.

Immobilized drug coatings. Coating of the stent surface with an antithrombotic agent such as heparin[40-42] provides a novel solution to the problem of increased thrombogenicity of metallic stents and the subsequent need for intensive anticoagulation that results in increased morbidity and costs. After encouraging preliminary experience with a heparin-coated Palmaz-Schatz stent in pig coronary arteries, the Bene-

stent-II study evaluated the safety of reducing and eliminating anticoagulant therapy in patients receiving a heparin-coated stent. Initial results from the pilot study suggest that subacute stent thrombosis does not occur using the heparin-coated stent, which virtually eliminated the bleeding complications after stent implantation and reduced the in-hospital stay to 3 days.[43] The 6-month angiographic follow-up examination also indicates that these coated stents do not induce excess of intimal hyperplasia.[44] The results of follow-up studies in which coumadin and heparin are replaced by ticlodipine and aspirin are awaited.

Polymer-coated stents. The stent metal surface can be rendered less thrombogenic by coating it with a thin layer of a synthetic polymer. Initial results suggested that, although this may protect against acute thrombotic events, it does not reduce the extent of subsequent neointimal hyperplasia.[45] However, the advantage of a polymer-coated stent is that it can be loaded with antithrombotic or antiproliferative agents directed against the neointimal reparative process (Fig 6).[46]

Fibrin stent. The fibrin-film stent has several theoretical advantages. It is a membrane stent and thus can cover the balloon angioplasty injury site, thereby providing a natural healing matrix while reducing local thrombus formation. It may also be useful in vein grafts in which the membrane may prevent distal embolization of friable material. Preliminary work suggests that the fibrin-film stent is both bioabsorbable and biocompatible.[47] It also appears to be safe in pigs with the use of an antiplatelet agent. However, it had little effect on neointimal proliferation.

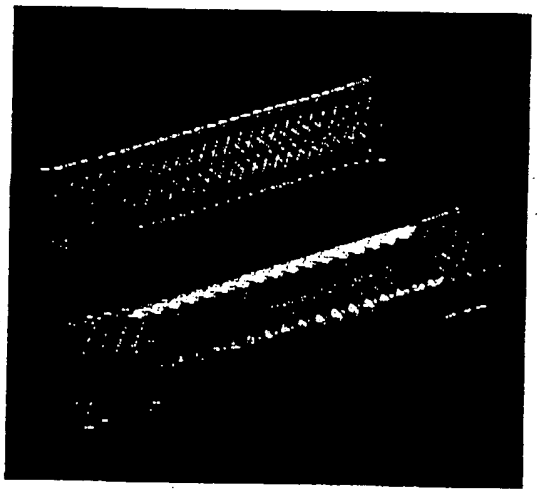

Fig 6. An eluting stent consisting of a stent surrounded by an elastic sleeve made of biodegradable polymer loaded with 40% antithrombotic agent is shown.

Vein-coated stents. An autologous vein graft-coated stent consisting of a conventional stent covered by a vein graft may be the ideal conduit for percutaneous revascularization, thus minimizing stent thrombogenicity and local tissue reaction to the stent. Preliminary experience in 13 patients suggests that the technique is feasible and safe, resulting in an excellent immmediate angiographic result,[48] but further studies are warranted to investigate the effect of the procedure on subacute thrombosis and long-term restenosis.

Nitinol Stent

Nitinol has a number of properties that make it ideal for stent composition. It is known to be highly biocompatible and highly malleable, allowing 0.006-in struts without sacrificing flexibility. Furthermore, it has unique thermoelastic properties that allow for stent collapse and removal as well as for self-expansion.[49-52] Finally, it is amenable to surface coating for local drug delivery and is transmutable into a radioactive emitter for local radiation therapy. Preliminary work in a pig coronary subacute thrombosis model has confirmed some of these theoretical advantages of a nitinol stent showing that nitinol stents, particularly polished nitinol stents, develop significantly less thrombus (as measured by thrombus weight and thrombus grade) in comparison with that for stainless steel stents of similar design.[49] The results on neointimal hyperplasia are still awaited, although preliminary results from a separate group suggest that a self-expanding nitinol stent exerts a more favorable effect on vascular remodeling and neointimal formation than does a balloon-expandable, tubular, slotted stent.[50] Initial experience in 20 patients suggests that a nitinol stent is safe and effective in the treatment of suboptimal results.[52]

Polymer Stent

Polymer stents have several potential advantages. They can be loaded with antithrombotic

and/or antiproliferative pharmaceutical agents in high concentration for sustained local delivery. They may have less of a mechanical mismatch with the vessel wall than do metal stents and may avoid the potential for late-stage complications. Therefore, polymer stents have a synergistic mechanical and local pharmacological effect that provides sustained structural support throughout the healing phase, thus potentially avoiding early and late elastic recoil while the local high-dose drug delivery potentially prevents thrombosis, neointimal proliferation, and systemic side effects. However, there is only limited strength if a large percentage of drug is loaded onto the stent. Initial animal experiments, however, have shown a marked inflammatory response resulting in substantial luminal encroachment with polymer stents in porcine coronary arteries.[53,54] However, there is no vascular tissue reaction with high molecular weight poly-l-lactic acid, and this remains a promising avenue of investigation.

Composite (Metal-Augmented) Polymer Stents

Composite polymer stents guarantee a minimal mechanical mismatch between the stent and the vessel wall, leaving a delicate metal skeleton after biodegradation. They provide protection of tissues from deep strut laceration and large amounts of drug (up to 40%) for slow local release without affecting hoop strength. Such a composite polymeric stent, capable of excellent mechanical strength as well high-dose local drug delivery, has been developed and evaluated in porcine coronary arteries. Preliminary histological analysis showed that neointimal hyperplasia and some degree of inflammatory response were present in all groups. Unfortunately, implantation of bicomponent stents caused a reduction in lumen diameter for all designs. Further research will assess the relative contributions of stent geometry, polymer type, and incorporated drug to the overall response.

Radioactive Stents

Radiation selectively kills proliferating cells independent of the stimulus for cell growth. Because a major cause of restenosis is neointimal hyperplasia secondary to vascular smooth muscle cell proliferation, it seems reasonable to assume that radiation therapy may reduce restenosis. Multiple animal studies have now confirmed the ability of radiation therapy to inhibit neointimal hyperplasia and reduce restenosis.[55,56] Radioactive stents have the potential to deliver an appropriate dose of radiotherapy to the area of interest, thus reducing restenosis while minimizing the total dose administered to the patient.

Two methods are currently in use. In the first method, conventional Palmaz-Schatz stents are bombard with ions in a cyclotron and subsequently emit low-dose β and γ radiation from radioisotopes Co55, 56, 57, Mn52, and Fe55, with half-lives between 17.5 hours and 2.7 years.[57] The radiation is predominantly short range, is homogeneously distributed over the length and circumference of the stent, and is absolutely fixed to the metal. For this reason, the stents do not require a license from the International Atomic Energy Agency (Vienna, Austria). An intimal surface dose rate of 4 mGy/h results in an integral dose of 180 mGy after a period of 100 days.

Low-dose radioactive stents were found to markedly inhibit neointimal hyperplasia in rabbits. Endothelialization of the radioactive stents was found to be delayed with macrophages being located on top of the radioactive stent struts until endothelialization was complete. Although the degree of neointimal hyperplasia was reduced, it was found, paradoxically, that extracellular matrix production increases after radioactive stent implantation.[57]

The second method is uses β particles.[58,59] β Particles (free electrons) may represent the ideal means of local irradiation. P^{32} is an excellent candidate for local delivery because the maximal range of β particles is 3 to 4 mm in tissue. It has a desirable half-life of 14.3 days, and, once implanted after balloon angioplasty, there is no detectable radiation by 4 months. P^{32} or other β emitters can also be implanted directly onto the stent wire.

Such P^{32}-impregnated stents have been now fabricated. In vitro work suggests that very low β-particle activity levels inhibit smooth muscle cell growth preferentially within a 5- to 7-mm radius of the P^{32}-coated stent wires, whereas endothelial cells appear to be much more radioresistant. In vivo animal testing in a porcine

restenosis model using low-dose rate P^{32} stents have shown inhibition of neointimal growth.[58]

A P^{32}-coated stent with doses similar to those described should be safe in humans. Total-body dosimetry to the patient would be less than 1/1000 that of fluoroscopy during angioplasty. Furthermore, the radiation would be local and would not reach any mediastinal tissues. Additionally, the radiation to the interventionalist will be much less than that occurring with fluoroscatter.

CONCLUSIONS

The stent represents the second generation of coronary angioplasty. It is a predictable therapy for bailout that improves a suboptimal result and reduces the risk of restenosis. As a result of these advantages, over 40% of coronary interventional procedures in the current year will include stent implantation. However, the currently available stents have a number of limitations that are being addressed. Drug-eluting stents that address the problem of the small vessel and low-flow situations are on the horizon. Covered stents in which a membrane acts as an isolating barrier that minimizes local thrombus formation and delivers local drug therapy are promising. Radioactive stents to inhibit local neointima formation are another promising avenue of investigation. Biodegradable stents and composite stents are also being actively investigated.

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Interventional Cardiology

Preventive effects of an antiallergic drug, pemirolast potassium, on restenosis after percutaneous transluminal coronary angioplasty

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Background We recently confirmed that pemirolast potassium, an antiallergic agent, markedly inhibits migration and proliferation of vascular smooth muscle cells. It has also been reported that pemirolast inhibits intimal hyperplasia in animal experiments.

Methods and Results To elucidate the preventive effects of pemirolast on restenosis after percutaneous transluminal coronary angioplasty (PTCA), 227 patients were enrolled in this prospective, randomized trial. A total of 205 patients who were compatible with the protocol were analyzed (pemirolast group, 104 patients with 140 lesions; control group, 101 patients with 133 lesions). Patients in the pemirolast group received 20 mg/d of pemirolast from 1 week before PTCA until the time of follow-up angiography (4 months after PTCA). Angiographic restenosis was defined as diameter stenosis ≥50% at follow-up. Restenosis rates were significantly lower in the pemirolast group than in the control group (24.0% vs 46.5% of patients, 18.6% vs 35.3% of lesions, $P < .01$, respectively). During 8 months of follow-up, there were no coronary events (death, myocardial infarction, coronary artery bypass surgery, or repeated PTCA) in 81.7% of the pemirolast group and in 63.4% of the control group ($P = .013$).

Conclusions This study suggested that pemirolast would be useful in the clinical setting to prevent restenosis after PTCA. (Am Heart J 1998;136:1081-7.)

Restenosis after percutaneous transluminal coronary angioplasty (PTCA) remains an important unsolved problem. Stenting has contributed to reduction of restenosis by preventing pathologic vascular remodeling,[1,2] but the proliferation of vascular smooth muscle cells (VSMC), one of the causes of restenosis, is observed even after stent placement.[3] Pharmacologic strategies that prevent the proliferation of VSMC in animals have been ineffective in human beings. Recently, the antiallergic and antikeloid drug tranilast was reported to be effective in preventing restenosis after PTCA[4,5] in Japan. Experimental studies have shown that tranilast particularly inhibits collagen synthesis[6] through the suppression of transforming growth factor (TGF)-β1,[7] which suggests that tranilast may prevent restenosis. On the other hand, we recently confirmed that pemirolast potassium,[8-12] an antiallergic agent widely used in Japan, markedly inhibits migration and proliferation of VSMC, mainly by inhibition of inositol phospholipid turnover, which is the initial stage of the intracellular signal transduction system.[13] The inhibitory effects of pemirolast on VSMC proliferation are found to be higher than those of tranilast (unpublished data).

Furthermore, it has been reported that pemirolast inhibits intimal hyperplasia in animal experiments.[14] On the basis of these results, we conducted a clinical prospective, randomized study to investigate the preventive effects of pemirolast on restenosis after PTCA.

Methods

Patient selection

The study population consisted of patients with symptomatic ischemic heart disease caused by de novo lesions of the native coronary artery. The specific angiographic criterion for enrollment was ≥75% stenosis to be dilated (classification of

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percentage of stenosis by the American Heart Association Committee Report[15]). The criteria for exclusion were acute myocardial infarction, left ventricular ejection fraction of ≤40%, and renal failure treated with hemodialysis. The angiographic criteria for exclusion were the presence of type C lesions[16] such as chronic total occlusion (≥3 months old), ostial lesions, diffuse lesions, and left main trunk lesions.

After the patients were interviewed to determine their eligibility and had been given informed consent, they were randomly and prospectively assigned to one of two groups: a group given pemirolast (pemirolast group) or a group not given pemirolast (control group).

Drug treatments

The pemirolast group was given 20 mg/d pemirolast, its standard dose as an antiallergic drug, from 1 week before PTCA until follow-up angiography 4 months later. All subjects in both groups were given aspirin (81 mg/d), nitrate, calcium antagonists, and/or β-blockers (selected at the discretion of attending physicians) from at least 1 week before the procedure to follow-up angiography 4 months later. Drugs for treating complications such as hypertension, hyperlipidemia, and diabetes mellitus were used at the discretion of attending physicians, but the use of other antiallergic drugs was prohibited.

Angioplasty protocol

Angioplasty was performed with the conventional techniques. Immediately before the procedure, patients received an initial bolus injection of heparin (8000 to 10,000 units) and intracoronary administration of 200 μg nitroglycerin. By using balloon angioplasty, investigators attempted to achieve an optimal result, which was defined as residual stenosis of <30% of the luminal diameter according to a visual estimate, without any complications (death, myocardial infarction, coronary artery bypass surgery [CABG], or bail-out stenting). Heparin and nitroglycerin infusions were continued for 24 hours after the procedure.

Follow-up

All treated patients were monitored for at least 8 months. Adverse effects attributable to pemirolast were monitored at the fixed periods (before administration and 1 day, 2 weeks, and 4 months after PTCA) by interview as well as by laboratory examinations. Coronary angiography was repeated 4 months after PTCA. If ischemic symptoms recurred within 4 months after PTCA, coronary angiography was performed earlier. If no definite restenosis was found, a subsequent angiography was repeated 4 months later.

Angiographic analysis

Coronary angiograms obtained before, immediately after, and 4 months after PTCA were reviewed by an unbiased angiographer without knowledge of group randomization. All views were recorded after intracoronary administration of nitroglycerin (200 μg). Lesions were visualized in multiple views and scored according to the presence of eccentricity, irregularity, calcification, thrombus, ulceration, and so on.

For quantitative analysis, end-diastolic cineframes were selected from the angiographic views demonstrating the maximal degree of stenosis and were matched before, immediately after, and at follow-up. The selected cineframes were digitalized with a cinevideo converter, and a computer edge-detection algorithm was applied to the arterial and catheter contours (Coronary analyzer system; PADL Co, Osaka, Japan). With the guiding and diagnostic catheters as the calibration standard, reference diameter, minimal lumen diameter, and percentage of diameter stenosis were calculated. Acute gain was defined as the increase in minimal lumen diameter immediately after PTCA, late loss as the decrease in minimal lumen diameter at follow-up (postprocedure minus follow-up minimal lumen diameter), and net gain as the difference between acute gain and late loss. Successful angioplasty was defined as the reduction of diameter stenosis to <50%. Angiographic restenosis was defined as a diameter stenosis ≥50% at the end of follow-up.

End points

The primary end point of the trial was angiographic evidence of restenosis at follow-up. Secondary end points were clinical: occurrence of acute closure, acute myocardial infarction, repeated PTCA, and CABG within the first 8 months after the initial PTCA. Event-free survival was defined as absence of death, myocardial infarction, or repeated revascularization by PTCA or CABG.

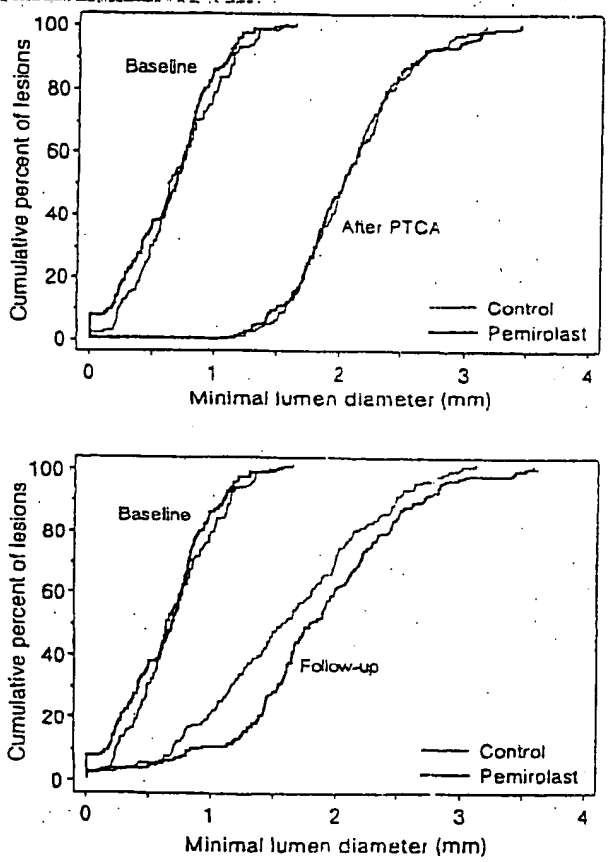
Statistical analysis

For the analysis of continuous variables, the Student's t test was used to assess differences between the pemirolast group and the control group. The results are expressed as mean ± SD. Categorical variables, which are presented as rates, were compared by chi-square test, except for the composite clinical end point and revascularization of the target lesion, which were analyzed by means of Kaplan-Meier survival curves, with differences between the 2 groups compared by Wilcoxon test. Statistical significance was defined as $P < .05$.

Results

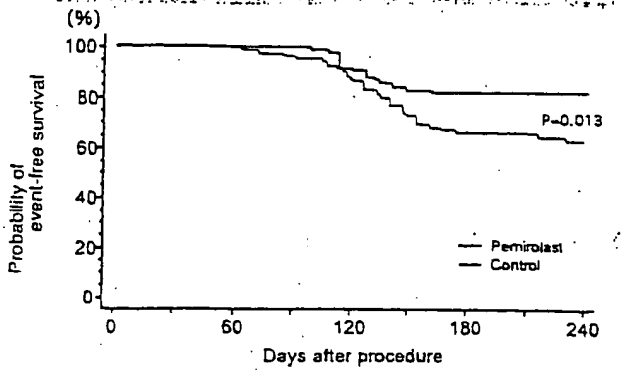
Between January 1994 and June 1996, 227 patients were enrolled in this study. Twenty-two of them were excluded from evaluation because of the failure or suboptimal results of PTCA (17 patients), deviation from the protocol (2 patients), or lack of follow-up angiography (3 patients). Thus the final study group comprised 205 patients, with 104 patients (140 lesions)

Figure 1



Cumulative frequency distribution curves.

Figure 2



Kaplan-Meier survival curves for major cardiac events (death, myocardial infarction, coronary artery bypass surgery, and repeated angioplasty).

in the pemirolast group and 101 patients (133 lesions) in the control group.

Baseline characteristics

Baseline clinical characteristics are shown in Table I, and baseline angiographic and procedure-related characteristics are shown in Table II. There were no significant differences in baseline characteristics between the 2 groups except for a higher incidence of chronic occluded lesions (<3 months old) in the pemirolast group than in the control group.

Angiographic results

The average time to follow-up angiography was 4.2 ± 0.7 months (pemirolast group: 4.0 ± 0.4 months; control group: 4.4 ± 0.8 months, not significant [NS]). Luminal dimensions at baseline, immediately after PTCA, and at follow-up are shown in Table III. At baseline, there were no differences between the 2 groups in reference diameter, minimal lumen diameter, or severity of stenosis. Immediately after PTCA, there were no differences in minimal lumen diameter, severity of stenosis, or acute gain between the 2 groups, whereas at follow-up the pemirolast group had a smaller mean reduction in minimal lumen diameter (late loss: 0.20 ± 0.61 vs 0.46 ± 0.57 mm, $P < .001$) and larger net gain (1.23 ± 0.68 vs 0.91 ± 0.62 mm, $P < .001$), resulting in a larger minimal lumen diameter (1.87 ± 0.70 vs 1.62 ± 0.68 mm, $P < .001$) and a lower severity of stenosis (33.6% ± 20.9% vs 43.6% ± 19.5%, $P < .001$). The cumulative distribution of the minimal lumen diameter is shown in Fig 1. Restenosis rates both per lesion and per patient in the pemirolast group were lower than those in the control group (18.6% vs 35.3% and 24.0% vs 46.5%, $P = .002$, respectively).

Clinical outcomes

The numbers of various types of clinical events at 8 months among all 205 patients are shown in Table IV. During follow-up no patient died in either group, but 1 patient in the control group had a non-Q-wave myocardial infarction caused by restenosis and received elective CABG. The incidence of recurrent angina was significantly lower in the pemirolast group than in the control group (6.7% vs 19.8%, $P = .012$). There was no significant difference in the incidence of a positive treadmill test between the pemirolast group and the control group (11.5% vs 16.8%). A repeated angioplasty was performed on

Table I. Baseline clinical characteristics

	Pemirolast (n = 104)	Control (n = 101)	P value
Male sex	78.8	75.2	NS
Age (mean ± SD years)	62 ± 10	61 ± 10	NS
Unstable angina	38.5	26.7	NS
History of myocardial infarction	41.3	39.6	NS
Hyperlipidemia	51.9*	46.5	NS
Hypertension	52.9	40.6	NS
Current smoker	41.3	35.6	NS
Obesity (body mass index ≥26)	29.8	30.7	NS
Diabetes mellitus	28.8	26.7	NS
Hyperuricemia	12.5	13.9	NS
Concomitant drugs			
Nitrates	88.5	85.1	NS
Antiplatelet agent (aspirin, 81 mg)	94.2	97.0	NS
Calcium channel blockers	76.0	72.3	NS
β-Blockers	46.2	50.5	NS
ACE inhibitors	20.2	15.8	NS
Antilipemic drugs (pravastatin or simvastatin)	26.9	20.8	NS
No. of target lesions per patient			NS
1	62.5	63.4	
2	22.1	29.7	
3	15.4	6.9	

Values are % of patients.

those patients who showed such ischemic signs. The incidence of repeat angioplasty was lower in the pemirolast group than in the control group (18.3% vs 36.6%, P = .005). In addition, 6 patients (5.8%) in the pemirolast group and 9 control patients (8.9%) in whom ischemic signs were not recognized were followed up medically. The results demonstrated that the event-free survival rate was significantly higher in the pemirolast group than in the control group (81.7% vs 63.4%, P = .013) (Fig 2).

A slight elevation of glutamic-pyruvic transaminase was observed in 1.9% (2 of 104) of patients 1 to 2 weeks after starting administration of pemirolast, but this returned to the baseline level after 2 weeks without interruption of administration. One of the 2 patients was positive for hepatitis C virus antibody. Neither symptoms nor significant aggravation of laboratory findings attributable to pemirolast were observed in the other 102 patients.

Discussion

Before our study, Kato et al[5] noted the similarity of reparative processes of vascular wall injury, VSMC proliferation, and extracellular matrix synthesis to the process of keloid formation and conducted multicenter, placebo-controlled, double-blind studies to elucidate the preventive effects of the antiallergic and antikeloid drug tranilast on restenosis after PTCA.[4,5] They reported that tranilast reduced clinical restenosis at 3 months after PTCA.[4]

In the current randomized comparative study, the antiallergic agent pemirolast was found to reduce not only the angiographic restenosis rate but also late cardiac events. Pemirolast is known to result in minor and infrequent adverse events in 3.6% of 112 patients (nausea: 0.9%, headache: 0.9%, exanthema: 0.9%, slight increase in number of platelets: 0.9%) in comparison with tranilast (12.4% of 113 patients).[12] A low incidence of adverse effects (1.9%) was confirmed in the current study. These results suggest that pemirolast has pharmacologic properties useful in preventing restenosis after PTCA.

However, the exact mechanisms are not known. The results of preclinical studies both in vitro[13] and in vivo[14] suggest that pemirolast reduces restenosis by preventing neointimal hyperplasia. In recent years, serial (after angioplasty and follow-up) intravascular ultrasound (IVUS) studies[17,18] have been performed to examine the restenosis process after PTCA, and it has been determined that 2 basic underlying mechanisms, namely neointimal proliferation and vascular remodeling, participate in restenosis. Further, it has been considered that neointimal hyperplasia is solely responsible for in-stent restenosis.[3,18] Our serial IVUS study in

Table II. Angiographic and procedure-related characteristics

	% of Lesions		
	pemirolast (n = 140)	control (n = 133)	P value
Target vessel			
Left anterior descending	44.3	45.9	NS
Left circumflex	28.5	27.8	NS
Right coronary artery	27.9	26.3	NS
With collaterals	18.6	17.3	NS
Infarct-related lesion	25.7	23.3	NS
Type of lesion			NS
Type A	26.4	30.1	
Type B	73.6	69.9	
Lesion morphology			
Concentric	28.6	32.3	NS
Eccentric	37.1	38.3	NS
Major branch involved	10.0	11.3	NS
Irregular contour	15.7	12.8	NS
Calcified	10.0	9.8	NS
Occluded (<3 months old)	11.4	4.5	.04
Thrombus	4.3	2.3	NS
Ulceration	5.7	4.5	NS
Dissection	2.1	1.5	NS
Lesion length (mm)	6.9 ± 3.4	6.5 ± 3.3	NS
Balloon/artery ratio	1.14 ± 0.18	1.14 ± 0.15	NS
Inflation of the largest balloon			
Frequency	3.1 ± 1.3	3.0 ± 1.2	NS
Maximal pressure (atm)	9.5 ± 2.1	9.5 ± 2.5	NS
Total inflation time (s)	213 ± 128	200 ± 86	NS

patients treated with balloon angioplasty documented that pemirolast does not prevent vascular remodeling but does prevent neointimal hyperplasia. Furthermore, a similar study in patients with stent placements supported the view that the inhibitory action of pemirolast on neointimal hyperplasia is responsible for restenosis prevention (unpublished data). Consequently, it is considered that concomitant therapy by stenting and with pemirolast is more useful for preventing restenosis.

VSMC proliferation and the production of extracellular matrix are the result of complex processes[19-21] involving cytokines such as growth factors, arachidonic acid metabolites, and endothelium-derived contraction factors. Consequently, inhibition of the intracellular signal transduction systems common to many cytokines is likely to result in the effective inhibition of VSMC proliferation. Up to now, 2 pathways for these intracellular signal transduction proliferation systems are known,[22] one of which involves membrane inositol phospholipid turnover[23] starting from the activation of receptor tyrosine kinase. We confirmed through molecular biologic testing that pemirolast markedly inhibits VSMC proliferation induced by platelet-derived growth factor, angiotensin II, or endothelin I. In addition, we found that pemirolast suppresses membrane inositol phospholipid turnover at an early stage of the intracellular signal transduction system, which suggests that this is one of the mechanisms by which the agent inhibits VSMC proliferation.[13] It has been reported that tranilast prevents VSMC proliferation and collagen synthesis through the suppression of TGF-β1.[6,7] However, it remains to be elucidated whether pemirolast also acts through the suppression of TGF-β1.

The first steps have just been taken toward elucidating the mechanisms by which tranilast and pemirolast inhibit restenosis and clarifying the exact mechanisms of their actions. The common pharmacologic characteristics of tranilast and pemirolast as antiallergic agents is that both compounds have activity in targeting mast cells. It is well known that mast cells exist abundantly in the vascular wall, especially in the adventitia, and that they secrete chymase, an angiotensin II–forming enzyme.[24-26]

Experimental studies have shown that angiotensin II promotes the proliferation of VSMC and extracellular

Table III. Angiographic analysis

	Pemirolast (n = 140)	Control (n = 133)	P value
Before the procedure			
Reference diameter (mm)	2.70 ± 0.56	2.70 ± 0.53	NS
Minimal lumen diameter (mm)	0.63 ± 0.35	0.71 ± 0.34	NS
Stenosis (%)	76.4 ± 11.9	74.7 ± 10.6	NS
After the procedure			
Minimal lumen diameter (mm)	2.07 ± 0.46	2.07 ± 0.42	NS
Stenosis (%)	21.4 ± 8.9	22.1 ± 8.9	NS
At follow-up			
Minimal lumen diameter (mm)	1.87 ± 0.70	1.62 ± 0.68	.003
Stenosis (%)	33.6 ± 20.9	43.6 ± 19.5	<.001
Change in minimal lumen diameter			
Acute gain (mm)	1.44 ± 0.52	1.37 ± 0.43	NS
Late loss (mm)	0.20 ± 0.61	0.46 ± 0.57	<.001
Net gain (mm)	1.23 ± 0.68	0.91 ± 0.62	<.001
Restenosis			
Lesions (%)	26/140 (18.6)	47/133 (35.3)	.002
Patients (%)	25/104 (24.0)	47/101 (46.5)	.002

Table IV. Cardiac events caused by restenosis during 8-month follow-up

	Pemirolast (n = 104)	Control (n = 101)	P value
Cardiac death	0	0	
Myocardial infarction	0	1 (1.0 %)	
Recurrent angina	7 (6.7%)	20 (19.8%)	.012
Electrocardiographic changes during exercise	12 (11.5%)	17 (16.8%)	
Neither angina nor electrocardiographic changes	6 (5.8%)	9 (8.9%)	
Repeated angioplasty	19 (18.3%)	36 (35.6%)	.005
Elective CABG	0	1 (1.0%)	

matrix by activating platelet-derived growth factor, TGF-β, basic fibroblast growth factor, and endothelin 1.[27,28] Injury to the intima of the carotid artery in dogs has been shown to lead to an increase in the number of mast cells in the adventitia and fibrotic outgrowth as well as intimal hyperplasia. Moreover, an increase in angiotensin II levels and a chymase level exceeding the angiotensin-converting enzyme (ACE) level were demonstrated in the injured vascular wall.[26]

Given these reports, it is important to examine the effects of pemirolast on the chymase-dependent angiotensin II–forming pathway, and we will perform further studies to elucidate the mechanisms by which pemirolast prevents restenosis

Limitations

Because this study was not a double-blind but an open study, a double-blind study must still be done. The most appropriate time to begin administration is an important issue to be determined. If VSMC proliferation begins in the first 24 hours after PTCA, as has been reported,[29] preprocedural administration is likely to be more effective. In this study, therefore, administration was started 1 week before PTCA. If efficacy is not affected, however, it would be sensible and desirable to begin administration after the procedure. Further studies are required to determine the ideal dosage, appropriate time to begin administration, and duration of administration to bring pemirolast into clinical use as a new preventive modality of restenosis.

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